## REMARKS

With entry of the instant amendment, claims 1, 4, and 5 have been amended and claims 2, 3, 6, and 8-21 have been cancelled. Claims 1, 4, 5, and 7 are therefore under examination.

Cancellation of subject matter is without prejudice to revival for prosecution in a continuation or divisional application.

The amendments to the claims add no new matter and are supported throughout the application as filed. Claim 1 has been amended to recite that the knockout mouse has a genome that comprises a disruption in each allele of the mouse's endogenous melanopsin gene. Support can be found, *e.g.*, at paragraph 53. Claims 4 and 5 have also been amended to simplify the claim language.

***Rejections under 35 U.S.C. § 112, first paragraph-enablement***

The claims were rejected as not properly enabled by the specification. In particular, with regard to claims 1 and 5, the Examiner alleges that the claims as filed read on a heterozygous mouse and that the specification does not provide adequate evidence to suggest a specific phenotype for a *Opn*+/- heterozygous mouse. With regard to claims 5-7, the Examiner contends that the specification provides inadequate guidance and/or working examples to show feasibility of a transgenic knockout animal other than a mouse. Specifically, the Examiner argues that it would require undue experimentation to generate such an animal. With regard to claims 3 and 5-8, the Examiner alleges that the claims are not enabled for a mouse that shows attenuated circadian rhythm phase shift in response to any type of light pulse during a dark portion of an environmental dark/light cycle.

First, although Applicants disagree with the rejections, in order to expedite prosecution, claims 1 and 5 have been amended. Claim 1 has been amended to recite that the genome of the knockout mouse comprises a disruption in each allele of the endogenous melanopsin gene. Claims 1 and 5 have been amended to incorporate the elements set forth in

claims 3 and 6, respectively. Claim 5 has also been amended to recite a transgenic knockout mouse.

Next, Applicants traverse the Examiner's allegation that the application enables only a transgenic mouse that exhibits a circadian rhythm phase shift in response to a monochromatic light pulse. The Examiner has not provided a proper showing that one of skill could not reasonably practice the invention based on the teachings in the specification.

The specification provides guidance beginning on page 12 for generating a knockout mouse, including teachings relating to techniques and vectors that can be employed. The specification additionally teaches use of various light pulses (*see, e.g.,* paragraphs 57 and 58) for testing circadian rhythm responses. For example, the specification teaches when a pulse of light may be introduced and how to monitor the effects of the pulse with respect to a marker of circadian rhythm (*see, e.g.,* paragraph 59). Paragraphs 100-101 and Figure 3 provide an exemplary embodiment in which melanopsin knockout mice exhibited a change in a marker of circadian rhythm response relative to wildtype mice. Thus, the disclosure in the specification provides ample guidance to a practitioner in this advanced art for making a melanopsin knockout mouse as claimed.

The Examiner appears to believe, however, that one of skill could not predictably use such a mouse because of alleged variability in the phenotype. Specifically, the Examiner contends that it is not apparent that a melanopsin knockout mouse would show an attenuated phenotype to any type of light pulse. As described above, the specification teaches that mice lacking functional melanopsin exhibit a change in phenotype of the circadian rhythm response in comparison to wildtype animals. Additional evidence demonstrating that a melanopsin knockout mouse can exhibit a phase shift in response to a light pulse other than a monochromatic light pulse is provided by Ruby *et al.*, in *Science* 298:2211-2213, 2002, a copy of which is provided as Appendix A attached hereto. Ruby *et al.* describe melanopsin knockout mice in which the phase-shift magnitude and period responses were significantly lower in knockout mice than in wild-type mice (*see, e.g.,* page 2212, the second sentence of the first full paragraph). This was in response to a bright light pulse (*see, e.g.,* page 2211, the last line of column two bridging to line six of column 3; and reference "17" of the **References and Notes** section on page 2213).

On page 11 of the Office Action, the Examiner cites Beaule *et al.* and Kavakli *et al.* as teaching that the effects of inactivating melanopsin function in mice are "marginal" (page 11, second to the last sentence of the Office Action). The Examiner further cites Kavakli *et al.* as suggesting that the differences in the magnitude of phase shifts observed in knockout mice may be due to differences between mouse strain backgrounds. The Examiner contends that Beaule *et al.* and Kavakli *et al.* therefore provide evidence that the art itself suggests that it would require undue experimentation to obtain a melanopsin knockout mouse having the claimed phenotype. Again, Applicants respectfully disagree. The Examiner's contention that Beaule *et al.* and Kavakli *et al.* describe that melanopsin has only a modest role in circadian rhythm response is not relevant to the enablement of the current claims.

First, the passages of Beaule *et al.* and Kavakli *et al.* cited by the Examiner both refer to the melanopsin knockout studies by Ruby *et al.*, *supra*; and Panda *et al.*, *Science* 298:2213-2216, 2002 (a post-filing publication of Applicants' work, which is provided as Exhibit B). Both Beaule *et al.* and Kavakli *et al.* acknowledge that these two studies, which use two different melanopsin mouse models, in fact show that mice lacking functional melanopsin exhibit a significant attenuation of phase-shift in response to a light pulse during a dark portion of an environmental dark/light cycle (*e.g.*, Beaule *et al.*, page 75, second column, first sentence of the first full paragraph; and Kavakli *et al*, page 488, column 2, lines 8-10 of the second paragraph). Further, both Ruby *et al.* and Panda *et al.* conclude that melanopsin plays a significant role in the magnitude of photic responses (*see, e.g.*, Ruby *et al,* abstract, p. 2211; and Panda *et al.*, abstract, p. 2213). Thus, the art in fact demonstrates that inactivation of melanopsin results in a phenotype related to circadian rhythm response.

Last, Kavalaki *et al.* provides no explanation as to why the difference in phase shifts observed in the melanopsin knockout mice in the independent studies of Ruby *et al.* and Panda *et al.* would be due to differences between mouse strain backgrounds. Indeed, in view of the cited art, the claimed phenotype is reproducible. Thus, the art cited by the Examiner does not provide proper evidence to support the Examiner's contentions that the claims are not properly enabled.

In view of the foregoing, one of skill in the art could reasonably predict that a melanopsin knockout mouse generated in accordance with the teachings in the specification would exhibit the phenotype set forth in the claims. Applicants therefore respectfully request withdrawal of the rejection.

***Rejection under 35 U.S.C. § 103, obviousness***

Claims 1, 2, and 4 are rejected as allegedly obvious over Provencio *et al.* (*J. Neurosci* 20:600-605, 2000) in view of Capecchi (U.S. Patent No. 5,464,764) and GenBank Accession Number AF_147789. The Examiner characterizes claims 1 as drawn to a transgenic mouse comprising a disruption in an endogenous melanopsin gene, such that no functional melanopsin protein is made is the cells of the mouse and claim 2 as further including homozygous deletion of the melanopsin gene. The Examiner notes that these claims (as filed) do not include an element relating to any phenotype. The Examiner alleges that given the teachings in the cited art, it would have been obvious to make a transgenic melanopsin knockout mouse in order to investigate the physiological role of melanopsin in circadian rhythms and that one of skill could reasonably expect that such a knockout mouse could be generated.

Applicants disagree with the Examiner; however, in the interests of expediting prosecution, claim 1 has been amended to recite a phenotype. Applicants therefore respectfully request withdrawal of the rejection.

## CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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